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(54) **SYSTEME DE SOLVANT POUR AMELIORER LA PENETRATION DE COMPOSES PHARMACEUTIQUES**

(54) **SOLVENT SYSTEM FOR ENHANCED PENETRATION OF PHARMACEUTICAL COMPOUNDS**

(57) Composition comprenant un composé pharmaceutique ou médicament topique et un système de solvant tamponné capable d'accroître la pénétration de ce médicament. Le système de solvant tamponné permet d'utiliser une quantité réduite de composé pharmaceutique sans diminution significative de l'efficacité de ce composé.

(57) A composition is described, consisting of a topically active pharmaceutical compound or drug and a buffered solvent system capable of enhancing the penetration of said drug. The buffered solvent system allows for a reduced amount of pharmaceutical compound in the composition without significantly altering the efficacy of said compound.

Solvent System for Enhanced Penetration of Pharmaceutical Compounds

Field of the Invention

This invention relates to pharmaceutical compositions whose penetration is capable of being enhanced. This includes, but is not limited to, topical compositions for the treatment of skin disorders wherein the topically active pharmaceutical compound or drug is normally a relatively insoluble (or "poorly soluble") weak acid or weak base, however, the drug may also be a soluble compound whose delivery characteristics can be altered. More specifically, this invention concerns the solubilizing capabilities of a buffered solvent system which makes it possible to significantly alter the dermal penetration of pharmaceutical compounds or drugs.

Background of the Invention

Seborrheic dermatitis is a skin disorder characterized by an abnormal increase in the proliferation of epidermal cells. This increase in skin cell production causes the formation of lesions on the surface of the skin. Though treatments vary, the use of imidazole antifungals is of particular interest to the present invention.

While its true cause is still a topic of debate, it has been suggested that seborrheic dermatitis can be

caused by a fungal infection, which is why imidazole antifungals are so effective in its treatment. Ford *et al.* in *British Journal of Dermatology* vol. 107, 691-695 (1982) describe ketoconazole as fungicidal against *Pityrosporum ovale* (*Pityrosporum orbiculare* or *Malassezia furfur*), an important etiologic factor in seborrheic dermatitis. U.S. Pat. No. 4,942,162 discusses the use of imidazole antifungals, specifically ketoconazole and clotrimazole, for the treatment of psoriasis and seborrheic dermatitis.

This treatment can come in one of two forms - oral and topical. U.S. Pat. No. 4,491,588 describes the use of ketoconazole and metronidazole for the treatment of seborrheic dermatitis in a composition formulated for oral administration. However, European Pat. Application No. 396,184 states that by topically applying ketoconazole for the treatment of dermatologic conditions, its efficacy and safety are enhanced. Furthermore, according to U.S. Pat. No. 4,446,145, it is best to avoid oral therapy for the treatment of skin diseases whenever a topical alternative is available.

Imidazoles, though potent when used as the sole active ingredient in a composition, can be combined with other pharmaceutical actives. World Pat. Application No. 87/04617 describes the combination of urea and imidazole

derivatives in a composition for the treatment of various skin disorders, however, urea causes temporary stinging sensation on the surface of users' skin. U.S. Pat. No. 4,446,145 describes the combination of an imidazole with benzoyl peroxide in compositions to be used specifically for the treatment of acne. Similarly, U.S. Pat. No. 5,002,938 describes a stable gel formulation for the topical administration of imidazoles, wherein the imidazoles are combined with a steroid, but seborrheic dermatitis is a chronic relapsing disease, therefore, the safety of the topical steroid preparations over a long period of time is questionable.

Another issue in the use of imidazoles is the delivery system. U.S. Pat. No. 5,219,877 describes a penetration enhancing gel for the topical administration of imidazoles, using lauryl alcohol as the penetration enhancer. The compositions described therein, however, specifically call for the omission of propylene glycol, whose solubilizing capabilities are well known in the art.

In fact, the combination of glycols with other solvents is a highly effective means of enhancing dermal penetration of actives. U.K. Pat. Application No. 2,202,743 utilizes the combination of propylene glycol and ethanol as a dissolving intermediary for the topical

administration of miconazole nitrate and econazole nitrate, but the composition described therein requires the presence of urea to solubilize the active ingredients. Similarly, Japanese Pat. No. 60-61518 uses a lower alcohol-glycol system for the topical administration of clotrimazole, but the composition described therein also requires both a neutralizer and a stabilizer.

The combination of a lower alcohol and a glycol is well known in the art as a reliable liquid carrier system. U.S. Pat. No. 4,994,491 uses this type of system for the treatment of cancer with trans-retinoids. The delivery capabilities of this combination are also exploited in U.S. Pat. No. 4,244,948 for the topical administration of acetylsalicylic acid, where the system is described as a "onvenient vehicle."

This system is employed in many antifungal products such as Exelderm® made by Westwood-Squibb Pharmaceuticals, Inc. (1% sulconazole nitrate), Monistat-Derm® available from Ortho Pharmaceutical Corporation (2% miconazole nitrate) and Oxistat® produced by Glaxo Wellcome, Inc. (1% oxiconazole nitrate). Similarly, U.S. Pat. No. 5,476,852 describes a 2% ketoconazole topical gel formulation which includes both propylene glycol and

ethanol. These products, however, require a high concentration of imidazoles (about one to two percent) to function properly. Another example is Nizoral®, a 2% ketoconazole antifungal cream made by Janssen Pharmaceutica, which contains a slightly different solvent system. This product, while quite effective, also requires a large percentage of ketoconazole.

It is therefore an objective of the present invention to create a composition capable of delivering the same therapeutic effect as current antifungal products at a significantly lower concentration of antifungal active.

It is also an objective of the present invention to create a solvent system which can be used to enhance the delivery of relatively insoluble pharmaceutical compounds which are weak acids or weak bases.

It is yet another objective of the present invention to create a solvent system which is capable of changing the penetration characteristics of readily soluble pharmaceutical compounds that are either acidic or basic.

Summary of the Invention

The present invention includes a buffered solvent system which is capable of changing the delivery parameters of both soluble and poorly soluble topically active pharmaceutical compounds or drugs. Surprisingly,

the addition of this buffering component to a properly balanced solvent system eliminates the need for excessive amounts of the pharmaceutical compound in topical compositions. In fact, a composition including this system only requires a fractional amount of the pharmaceutical compound necessary in products which lack this system. This is truly important because it addresses the problem of lack of clinical efficacy which has plagued these topical compositions for so long.

The system comprises a volatile solvent component, a nonvolatile solvent component and a buffer in addition to the topically active pharmaceutical compound or drug. Topical compositions of this nature generally contain such optional ingredients as chelators, antioxidants, preservatives, gelling agents and sunscreens as well as others commonly used in the art.

Brief Description of the Drawings

The present invention will become more readily apparent from the information in the following figures, which illustrate several characteristics of the preferred embodiments.

Figure 1 is a graphical summary of the skin permeability results from experimental Runs 1 through 4 in the formulation of ketoconazole, propylene glycol, ethanol and phosphate-citrate buffer.

Figure 2 is a graphical summary of the skin permeability results from experimental Run 6 in the occluded formulations of ketoconazole.

Figure 3 is a graphical summary of the skin permeability results from experimental Run 7 in the gel formulations of ketoconazole under both occluded and nonoccluded conditions.

Detailed Description of the Invention

The present invention is embodied in a topical composition comprising:

a) a topically active pharmaceutical compound or drug, and

b) a buffered solvent system comprising:

i) a volatile solvent component,

ii) a nonvolatile solvent component, and

iii) a buffer.

The topically active pharmaceutical compound or drug used in the compositions of this invention may be chosen from two categories: soluble and poorly soluble. Poorly soluble compounds may be further categorized as weak acids and weak bases.

Weak bases include such compounds as imidazoles, triazoles, steroidal anti-inflammatory agents, other antifungal drugs and the like.

The preferred imidazoles and triazoles include, but are not limited to, ketoconazole, miconazole, econazole, itraconazole, terconazole, saperconazole, fluconazole, metronidazole, clotrimazole, butoconazole, oxiconazole, sulfaconazole, sulconazole and their derivatives. The most preferred pharmaceutical compound selected from this group is ketoconazole. As elucidated in the Examples to follow, the imidazoles and triazoles are preferably in an amount of from about 0% (w/v) to about 1% (w/v) and more preferably from about 0.1% (w/v) to about 0.3% (w/v).

Suitable steroidal anti-inflammatory agents may include, although are not limited to, corticosteroids such as hydrocortisone, dexamethasone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone sodium phosphate, beclomethasone dipropionate, clobetasol valerate, desonide, desoxymethasone, desoxycorticosterone acetate, dichlorisone, diflorasone diacetate, diflucortolone valerate, flurandrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluocinolone acetonide, fluocinonide, fluocortin butyl ester, fluocortolone, fluprednidene (fluprednylidene) acetate, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone,

difluorosone diacetate, flurandrenolone acetonide, medrysone, amciafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chloroprednisone acetate, clocortolone, clescinolone, dichlorisone, difluprednate, flucloronide, flunisolide, fluorometholone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, betamethasone dipropionate, triamcinolone, and mixtures thereof may be used. The preferred steroidal anti-inflammatory agents are dexamethasone and its derivatives, while dexamethasone sodium phosphate is most preferred. The steroidal anti-inflammatory agents are preferably present in an amount of from about 0% (w/v) to about 5% (w/v).

Other antifungal drugs can be chosen from the group consisting of morpholine and its derivatives and terbinafine and its derivatives. Preferred pharmaceutical compounds are amorolfine and its derivatives, while amorolfine hydrochloride is most preferred. These antifungal drugs are preferably present in an amount of from about 0% (w/v) to about 5% (w/v).

Weakly acidic compounds useful in the compositions of this invention may be selected from the group

consisting of non-steroidal anti-inflammatory agents (NSAID's). These include, but are not limited to, oxicams, salicylates, acetic acid derivatives, fenamates, propionic acid derivatives, pyrazoles and mixtures thereof. Preferred examples of weak acids suitable for use in the present invention are salicylic acid, ibuprofen and indomethacin though many other appropriate weak acids exist. These weakly acidic compounds are preferably present in an amount of from about 0.1% (w/v) to about 10% (w/v).

Soluble pharmaceutical compounds or drugs can be either acidic or basic, wherein the buffered solvent system changes the permeability parameters of these compounds to enhance their delivery characteristics and efficacy. Soluble pharmaceutical compounds include, for example, alpha hydroxy acids. Preferred are alpha hydroxy acids selected from the group consisting of alkyl hydroxycarboxylic acids, aralkyl and aryl 2-hydroxycarboxylic acids, polyhydroxy-carboxylic acids and hydroxy-polycarboxylic acids. Most preferred are those alpha hydroxy acids selected from the group consisting of glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, their derivatives and mixtures thereof. Preferably, the soluble pharmaceutical compounds are

present in an amount of from about 4% (w/v) to about 15% (w/v).

The volatile solvent component of the buffered solvent system may preferably include lower (C_1-C_6) alkyl alcohols, lower alkyl glycols and lower glycol polymers. More preferably, the volatile solvent is selected from the group consisting of ethanol and isopropanol. Most preferably, the volatile solvent is ethanol. The volatile solvent component is thought to act as a penetration enhancer, while also producing a cooling effect on the skin as it evaporates. The amount of volatile solvent in the system is determined by the pharmaceutical compound being utilized, depending upon the solubility and skin penetration of said topically active pharmaceutical compound or drug. The criteria which limit the range of the volatile solvent remain the same, regardless of which pharmaceutical compound or drug is used. Too little volatile solvent in the system will render the drug insoluble, while an excess of the volatile solvent may cause irritation to the skin.

The nonvolatile solvent portion of the buffered solvent system is selected from lower alkylene glycols and lower glycol polymers. Preferably, propylene glycol, polyethylene glycol and polypropylene glycol may be used. Most preferably, propylene glycol is used. The

nonvolatile solvent slows the evaporation of the volatile solvent and reduces the vapor pressure of the buffered solvent system. The amount of this nonvolatile solvent component, as with the volatile solvent, is determined by the pharmaceutical compound or drug being used. When too little of the nonvolatile solvent is in the system, the pharmaceutical compound may crystallize due to evaporation of volatile solvent, while an excess will result in a lack of bioavailability due to poor release of drug from solvent mixture.

The buffer component of the buffered solvent system may be selected from any buffer commonly used in the art. The purpose of the buffer component is to ensure that the pharmaceutical compound or drug mostly remains in unionized state. The choice of buffer is only limited by its ability to adjust the pH of the system to be at least about 0.5 units below the pKa of the pharmaceutical compound when the pharmaceutical compound is a weak acid, and at least about 0.5 units above the pKa of the pharmaceutical compound when the pharmaceutical compound is a weak base. Once again, the pharmaceutical compound or drug being used dictates the type and amount of buffer needed for the system to function properly. Some preferable buffers include citrate, phosphate and borate buffers and combinations thereof.

There are several optional ingredients which can be added to the topical composition. These include, but are not limited to, chelators, antioxidants, preservatives, gelling agents, sunscreens, sunblocks, retinoids, benzofuran derivatives, N-acetyl-L-cysteine and derivatives thereof, skin protectants and vitamins. The preferred antioxidant is butylated hydroxytoluene (BHT), though ascorbic acid and its derivatives and vitamin E and its derivatives are also among suitable agents that may be employed as discussed in *Remington's Pharmaceutical Sciences*, Gennaro, A. R. (Editor), 18th edition 1990. Mack Publishing Co., Easton, PA. pp. 1286 - 1288. which is hereby incorporated by reference. Similarly, appropriate gelling agents can include, but are not limited to, semisynthetic cellulose derivatives and synthetic polymers. Preferably, the gelling agent is hydroxypropylcellulose. The preservatives can be selected from those common in the art as discussed in *The Theory and Practice of Industrial Pharmacy*, Lachman, L., Lieberman, H. A., and Kanig, J. L. 3rd edition, 1986. Lea & Febiger, Philadelphia, PA. pp. 467, 521 and 553, which is also incorporated by reference, though the parabens, especially methylparaben and propylparaben, are preferred. Preferred chelators include EDTA and citric acid, though EDTA is most preferred.

Suitable sunscreens may include, for example: p-aminobenzoic acid (PABA), its salts and its derivatives, anthranilates, salicylates, cinnamic acid derivatives, dihydroxycinnamic acid derivatives, trihydroxycinnamic acid derivatives, hydrocarbons, dibenzalacetone and benzalacetophenone, naphthol-sulfonates (sodium salts of 2-naphthol-3, 6-disulfonic and of 2-naphthol-6, 8-disulfonic acids), dihydroxynaphthoic acid and its salts, o- and p- hydroxybiphenyldisulfonates, coumarin derivatives, quinine salts, quinoline and its derivatives, uric and vilouric acids, tannic acid and its derivatives, hydroquinone, benzophenones and the hydroxy- or methoxy- substituted benzophenones, 4-isopropyldibenzoylmethane, butylmethoxydibenzoylmethane and etocrylene. Most preferred sunscreens useful in the compositions of the present invention are 2-ethylhexyl-p-methoxycinnamate, butylmethoxydibenzoylmethane, 2-hydroxy-4-methoxybenzophenone, octyldimethyl-p-aminobenzoic acid and mixtures thereof.

The key to the present invention, however, is the ratio of volatile solvent to nonvolatile solvent to buffer in the buffered solvent system. As evidenced by the Examples to follow, when this system is used in combination with ketoconazole as the topically active pharmaceutical compound, the preferred ratio of

ingredients is about 5% to about 15% of the nonvolatile solvent, from about 40% to about 45% of the volatile solvent and from about 45% to about 50% of the buffer. The requisite concentration of ketoconazole is only about 0.3% when this system is utilized, compared with values seven times that much in commercial compositions which lack this system.

The ratio of the components in the buffered solvent system depends upon the solubility characteristics of the pharmaceutical compound or drug under consideration. The composition may take the form of a solution, gel, lotion, cream, ointment, and the like. Following are several examples which are meant to illustrate possible embodiments of the present invention.

EXAMPLE 1

Topical Formulation of 0.3% Ketoconazole Solution and Gel

Chemically, ketoconazole is (±) cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine and has the following structural formula:

A 0.3% ketoconazole gel was made by first preparing a 0.1 μ pH 6.00 phosphate-citrate buffer. Disodium EDTA was dissolved into the buffer. Methylparaben, propylparaben, BHT and ketoconazole were dissolved in ethanol. Propylene glycol was then added to the ethanol solution and mixed well. The buffer containing EDTA was then added. Hydroxypropylcellulose (Klucel HF) was slowly added to the solution while stirring. The gel was allowed to hydrate for 24 hours and the final pH was adjusted to 7.00 using 1M HCl.

EXAMPLE 2

0.3% Ketoconazole Compositions

Thirteen solutions of 0.3% ketoconazole were prepared in varying proportions of propylene glycol, ethanol and buffer solution. The compositions are outlined in Table 1 below.

Table 1: Solvent Compositions

Composition	Propylene Glycol (ml)	Ethanol (ml)	Buffer (ml)	pH
A	60	20	20 - water	8.88
B	40	40	20 - water	8.36
C	20	60	20 - water	7.89
D	20	40	40	6.00
E	20	40	40	7.00
F	20	40	40	8.00
G	20	60	20	7.00
H	10	60	30	7.00
I	30	30	40	7.00
J	5	45	50	7.00
K	5	55	40	7.00
L	0.01M HCl solution			4.00
M	15	40	45	7.00

In compositions A, B and C, the aqueous phase was water, without a buffer, while in all of the other compositions (with the exception of composition L) the buffer was a phosphate-citrate buffer system. In composition L, hydrochloric acid was used as the solvent system.

EXAMPLE 3

Permeation Studies of 0.3% Ketoconazole Compositions

Permeability of ketoconazole from solutions A through M as defined in Example 2 was studied across

human cadaver skin using Franz diffusion cells. The Franz diffusion cell consisted of an upper donor cell and a lower receiver cell, wherein the skin was placed between them. The donor cell was an open cap, allowing access to the epidermis for dosing or other purposes. The test material/formulation was placed on the epidermal surface in the donor cell. The donor cell was left open to the atmosphere under nonoccluded conditions, and tightly sealed under occluded conditions. The donor and receiver cells were held together with a clamp. The capacity of the receiver cell was 10 ml, and the cross-sectional area of the cells in contact with the skin was 0.6362 cm^2 (0.9 cm diameter). A thermal jacket was positioned around the receiver chamber and was heated with an external circulating water bath. A Teflon coated stirring bar was placed in the receiver chamber and an isotonic phosphate-citrate buffer of pH 5.00 was used as a receptor solution to fill this chamber. During the course of an experiment, small volumes of the receptor solution were drawn from the chamber for analysis and replaced to keep the volume of the solution constant.

Three diffusion cells were used to evaluate each solvent composition and the cells were occluded (except where stated otherwise). At the end of a 48 hour experimental run, the skins were separated into epidermis

and dermis, extracted with 10 ml of methanol and assayed for ketoconazole content. The permeability results are set forth in Table 2.

Table 2: Permeability Results for Compositions A Through M

(values normalized to 1% ketoconazole strength)

Solvent Composition (PG:Ethanol:Aq Phase)	pH	Amount Permeated up to 36 hours (µg)	Amount in Epidermis (µg)	Amount in Dermis (µg)
A (60:20:20 H_2O)	8.88	11.13	8.07 ± 6.60	1.83 ± 1.87
B (40:40:20 H_2O)	8.36	2.03	6.13 ± 1.23	3.17 ± 1.40
C (20:60:20 H_2O)	7.89	5.03	23.03 ± 25.73	7.00 ± 8.53
D (20:40:40 Buffer)	6.00	22.63	15.07 ± 1.33	8.67 ± 3.60
E (20:40:40 Buffer)	7.00	29.87	22.53 ± 3.87	12.10 ± 3.47
F (20:40:40 Buffer)	8.00	21.53	16.53 ± 8.13	8.83 ± 4.27
G (20:60:20 Buffer)	7.00	39.27	47.67 ± 40.40	25.13 ± 13.87
H (10:60:30 Buffer)	7.00	136.60	89.80 ± 31.37	48.27 ± 20.97
I (30:30:40 Buffer)	7.00	41.40	60.47 ± 41.97	25.20 ± 19.83
J (5:45:50 Buffer)	7.00	133.47	219.27 ± 90.67*	55.10 ± 20.90
K (5:55:40 Buffer)	7.00	143.60	353.93 ± 121.13*	38.73 ± 1.97
L (0.01M HCl)	4.00	64.77	339.47 ± 106.73*	27.30 ± 18.33
J Gel - Nonoccluded (5:45:50 Buffer)	7.00	5.23	32.63 ± 10.37	11.37 ± 1.30
M Gel - Nonoccluded (15:40:45 Buffer)	7.00	2.83	24.73 ± 2.00	8.30 ± 1.27
2% Nizoral® cream Nonoccluded	7.60 - 7.75	0.47	15.41 ± 4.85	1.98 ± 1.02
J Gel - Occluded	7.00	46.43	83.47 ± 4.10	41.77 ± 10.40
J Gel - Nonoccluded	7.00	3.17	47.87 ± 17.97	5.37 ± 2.07
M Gel - Occluded	7.00	9.80	53.37 ± 13.60	18.90 ± 9.00
M Gel - Nonoccluded	7.00	2.03	29.70 ± 4.13	2.83 ± 1.10

* The epidermal blotting technique is not consistent with the previous runs. The drug levels in the dermis seem to be reasonable.

In experimental Run 1 (compositions A, B and C), solutions of ketoconazole were prepared in varying proportions of propylene glycol, ethanol and water. In experimental Run 2 (compositions D, E and F), the final

pH of the ketoconazole buffered solutions was adjusted to 6.00, 7.00 or 8.00 using 1 M HCl. In experimental Run 3 (compositions G, H and I), the pH of maximum permeability and retention in the skin layers (pH 7.00) was selected from Run 2, and propylene glycol, ethanol and buffer compositions were varied. In experimental Run 4 (compositions J, K and L), propylene glycol composition was fixed at 5%, and ethanol and pH 7.00 buffer compositions were varied in compositions J and K. The permeability of ketoconazole from compositions J and K was compared with the permeability of ketoconazole in hydrochloric acid (composition L) described in U.S. Pat. No. 4,569,935. The pH of the drug solution L was 4.00.

Based upon the results from Runs 1 to 4, solvent compositions J, H and K had maximum permeabilities and retention in the skin. This is shown in Figure 1, a graph of the cumulative amount of ketoconazole which permeated the skin over time. After 48 hours, compositions J, H and K had more than twice the permeability of other compositions.

Since a high amount of alcohol in the formulation can irritate the sensitive skin of patients with seborrheic dermatitis, compositions J and M , which had lesser amounts of alcohol were preferred. Other solvent

compositions with less ethanol were tried, but 0.3% ketoconazole formed suspensions in those compositions.

Table 3: Compositions in which 0.3% Ketoconazole Formed Suspensions

Composition	Propylene Glycol (ml)	Ethanol (ml)	pH 7.00 Buffer (ml)
I	5	40	55
II	10	30	60
III*	10	40	50
IV	15	30	55

* partially soluble

As described in Table 3, 0.3% ketoconazole forms a solution only in certain proportions of solvent mixture. To make a 0.3% ketoconazole solution, either the ethanol content should be greater than 40% or the propylene glycol content should be greater than 10%, wherein the buffer makes up the rest of the composition. Within this range of concentrations, the composition functions with minimal irritation and acceptable levels of bioavailability while being physically stable.

EXAMPLE 4

Preparation of Ketoconazole Gel Compositions

Solvent compositions J and M were modified with the addition of a chelating agent, an antioxidant and preservatives to prepare gels. They were prepared by first dissolving BHT, methylparaben and propylparaben in ethanol, and then adding propylene glycol and phosphate-citrate buffer containing disodium EDTA. These solutions were then gelled with 2% w/v of hydroxypropylcellulose

(high viscosity grade) and adjusted to pH 7.00, the pH of maximum skin penetration and retention, which is also the pH of maximum chemical stability for ketoconazole.

Table 4: Solvent Compositions J and M - Modified to Prepare Gels

Ingredient	Composition J	Composition M
Propylene Glycol	5 ml	15 ml
Ethanol	45 ml	40 ml
0.1 μ pH 6.00 Phosphate-Citrate Buffer (with 0.05% w/v disodium EDTA)	50 ml	45 ml
BHT	50 mg	50 mg
Methylparaben	200 mg	200 mg
Propylparaben	20 mg	20 mg

In experimental Run 6, ketoconazole gels of formulations J and M were compared with the permeability of ketoconazole from 200 mg of Nizoral® cream under nonoccluded conditions. In experimental Run 7, ketoconazole gels J and M were studied for permeability across the human cadaver skin under both occluded and nonoccluded conditions. The data from experimental Run 5 is not analyzed as the skin samples used to test permeability were found to be defective. As shown in Figure 2, Run 5 compared occluded compositions of Nizoral, J, K and M.

Figure 3 is a graph of Run 7 depicting the cumulative amount of ketoconazole which permeated the skin over time. Under occluded conditions, Gel J had somewhat better permeation abilities than Gel M. Under

nonoccluded conditions, however, the two gel formulations behaved similarly.

The unbuffered drug solutions shown in Run 1 (natural pH 7.89 to 8.88), with water as one of the components, had lower permeabilities and lower amounts of drug in the skin than the compositions of Gels J and M. The same is true for ketoconazole in the 0.01M hydrochloric acid solution (Composition L) which was less permeable and less retained in the dermis than from the propylene glycol, ethanol and pH 7.00 buffer solvent mixtures.

Permeability and retention of ketoconazole in the skin layers increased with decreased percentage of propylene glycol in the solvent. This could have been due to poor release of ketoconazole from higher propylene glycol proportions. Compositions H, J and K with 5 to 10% propylene glycol had maximum permeability and skin retention suggesting that the buffered solvent system had reached its maximum thermodynamic activity for ketoconazole.

Permeability results from Runs 6 and 7 indicate that the occluded cells have higher permeabilities and higher drug levels in the skin than the nonoccluded cells. The ketoconazole levels in receiver cells and skin layers for J and M gels in nonoccluded cells are comparable to those

of Nizoral® cream even though, the gels had only 1/7 of the ketoconazole strength of Nizoral® cream. These levels will be higher in seborrheic dermatitic skin which is more permeable than normal skin.

EXAMPLE 5

Thermal Stability Analysis of 0.3% Ketoconazole Compositions

An accelerated thermal stability analysis was performed on gel formulations J and M at 30°C (sampling time 16 weeks), 40°C (sampling times 8 and 16 weeks), and 50°C (sampling times 4, 8, 13 and 16 weeks). The samples were filled into glass vials and placed at appropriate temperatures. The data in Table 5 indicates that the drug is highly stable in both the formulations. Less than 5% degraded in 16 week samples stored at 50°C. A slight pink color was observed in 13 and 16 week samples studied at 50°C.

Table 5: Stability Results of 0.3% Ketoconazole Gel Formulations at pH 7.00 (Percentage Remaining)

Comp.	Initial	4 wks	8 wks		13 wks		16 wks	
		50°C	40°C	50°C	50°C	30°C	40°C	50°C
J	100	97.08	98.51	97.08	97.09	99.65	98.44	95.77
M	100	97.70	98.67	96.86	97.79	99.77	98.61	97.09

EXAMPLE 6

Solubility of Non-Steroidal Anti-Inflammatory Drugs (NSAID's)

Salicylic acid, ibuprofen and indomethacin are all poorly soluble in water. While their solubilities are better in pure ethanol [37% (w/v), 100% (w/v) and 2.0% (w/v) respectively], the problems of dermal irritation described earlier become an issue. When placed in two extreme buffered solvent systems of propylene glycol, ethanol and 0.1 μ phosphate-citrate buffer of pH 6.00, their solubilities are as outlined in Table 6.

Table 6: Solubilities of NSAID's

NSAID	Solubility in 10:80:10 (PG:Ethanol:Buffer)	Solubility in 80:10:10 (PG:Ethanol:Buffer)
Salicylic acid	35% w/v	20% w/v
Ibuprofen	70% w/v	20% w/v
Indomethacin	1.5% w/v	1.0% w/v

The ibuprofen was supplied by Spectrum Chemical Mfg. Corp., Gardena, CA. The indomethacin was supplied by Sigma Chemical Co., St. Louis, MO and the salicylic acid was supplied by Sigma Chemical Co., St. Louis, MO.

EXAMPLE 7

Solubility of Steroidal Anti-Inflammatory Drugs

Hydrocortisone solubility is 1.27% (w/v) in propylene glycol, 2.50% (w/v) in ethanol and 0.028% (w/v) in water. Betamethasone dipropionate is sparingly soluble in ethanol (1 gram dissolves in 30 to 100 ml), and practically insoluble in water (1 gram dissolves in more than 10,000 ml). The solubility of two steroidal anti-inflammatory drugs was studied in two extreme

buffered solvent systems of propylene glycol, ethanol and 0.1 μ phosphate-citrate buffer of pH 6.00 in the compositions outlined in Table 7.

Table 7: Solubilities of Steroidal Anti-Inflammatory Drugs

Anti-Inflammatory Drug	Solubility in 10:80:10 (PG:Ethanol:Buffer)	Solubility in 80:10:10 (PG:Ethanol:Buffer)
Hydrocortisone	2.5% w/v	1.5% w/v
Betamethasone dipropionate	3.0% w/v	0.75% w/v

Both the hydrocortisone and betamethasone dipropionate were supplied by Spectrum Chemical Mfg. Corp., Gardena, CA.

EXAMPLE 8

Solubility of Amorolfine

Amorolfine is a morpholine derivative applied topically as the hydrochloride salt in the treatment of fungal nail and skin infections. A 0.25% cream is applied once a day to treat skin infections, including various forms of tinea. For the treatment of nail infections caused by dermatophytes, yeasts and molds, a lacquer containing the equivalent of 5% amorolfine is painted onto the affected nail once or sometimes twice a week until the nail has regenerated. Amorolfine base is poorly soluble, though its hydrochloride salt should be soluble to an extent of greater than 5% in water and ethanol based upon its chemical structure.

EXAMPLE 9

Solubility of Alpha Hydroxy Acids

Alpha hydroxy acids (AHAs) are highly soluble in aqueous solutions throughout the pH range. Their solubility was studied in two extreme solvent compositions, propylene glycol : ethanol : 0.1 μ phosphate-citrate buffer of pH 6.00 at 10:80:10 and 80:10:10. The approximate solubilities are given in Table 8.

Table 8: Approximate Solubilities of AHA's

Alpha Hydroxy Acid	Solubility in 10:80:10 (PG:Ethanol:Buffer)	Solubility in 80:10:10 (PG:Ethanol:Buffer)
Glycolic acid	> 20% w/v	18% w/v
Lactic acid	> 20% w/v	>20% w/v
Malic acid	19% w/v	10% w/v
Tartaric acid	10% w/v	8% w/v
Citric acid	16% w/v	10% w/v

While the present invention has been illustrated by several examples of possible embodiments, it should be understood that these are not limiting.

What is claimed is:

1. A topical composition comprising:

a) a topically active pharmaceutical compound or drug, and

b) a buffered solvent system comprising:

i) a volatile solvent component,

ii) a nonvolatile solvent component, and

iii) a buffer component which functions to maintain the pH of the composition such that the pharmaceutical compound remains mostly in unionized state.

2. A topical composition in accordance with claim 1 wherein said topically active pharmaceutical compound or drug is a weak base which is poorly soluble in water.

3. A topical composition in accordance with claim 1 wherein said topically active pharmaceutical compound or drug is a weak acid which is poorly soluble in water.

4. A topical composition in accordance with claim 2 wherein said topically active pharmaceutical compound or drug is selected from the group consisting of imidazoles, triazoles, steroidal anti-inflammatory agents and other antifungal drugs.

5. A topical composition in accordance with claim 4 wherein said topically active pharmaceutical compound or drug is from about 0.01% (w/v) to about 5% (w/v).

6. A topical composition in accordance with claim 5 wherein said topically active pharmaceutical compound or drug is an imidazole or a triazole.

7. A topical composition in accordance with claim 6 wherein said topically active pharmaceutical compound or drug is selected from the group consisting of ketoconazole, miconazole, econazole, itraconazole, terconazole, saperconazole, fluconazole, metronidazole, clotrimazole, butoconazole, oxiconazole, sulfaconazole, sulconazole, terbinafine and derivatives thereof.

8. A topical composition in accordance with claim 7 wherein said topically active pharmaceutical compound or drug is from about 0% (w/v) to about 1% (w/v) ketoconazole.

9. A topical composition in accordance with claim 5 wherein said topically active pharmaceutical compound or drug is a steroidal anti-inflammatory agent.

10. A topical composition in accordance with claim 9 wherein said topically active pharmaceutical compound or drug is dexamethasone sodium phosphate.

11. A topical composition in accordance with claim 5 wherein said topically active pharmaceutical compound or drug is selected from the group consisting of amorolfine and its derivatives.

12. A topical composition in accordance with claim 11 wherein said topically active pharmaceutical compound or drug is amorolfine hydrochloride.

13. A topical composition in accordance with claim 3 wherein said topically active pharmaceutical compound or drug is a non-steroidal anti-inflammatory agent.

14. A topical composition in accordance with claim 13 wherein said topically active pharmaceutical compound or drug is from about 0.1% (w/v) to about 10% (w/v).

15. A topical composition in accordance with claim 14 wherein said topically active pharmaceutical compound or drug is selected from the group consisting of salicylic acid, ibuprofen and indomethacin.

16. A topical composition in accordance with claim 1 wherein said topically active pharmaceutical compound or drug is readily soluble in water.

17. A topical composition in accordance with claim 16 wherein said topically active pharmaceutical compound or drug is an alpha hydroxy acid.

18. A topical composition in accordance with claim 17 wherein said topically active pharmaceutical compound or drug is from about 4% (w/v) to about 15% (w/v).

19. A topical composition in accordance with claim 18 wherein said topically active pharmaceutical compound or drug is selected from the group consisting of glycolic

acid, lactic acid, malic acid, tartaric acid, citric acid, their derivatives and mixtures thereof.

20. A topical composition in accordance with claim 1 wherein said volatile solvent component is a lower (C_1-C_6) alkyl alcohol.

21. A topical composition in accordance with claim 20 wherein said volatile solvent component is selected from the group consisting of ethanol and isopropanol.

22. A topical composition in accordance with claim 21 wherein said volatile solvent component is ethanol.

23. A topical composition in accordance with claim 1 wherein said nonvolatile solvent component is selected from the group consisting of lower alkylene glycols and their derivatives and lower glycol polymers.

24. A topical composition in accordance with claim 23 wherein said nonvolatile solvent component is selected from the group consisting of propylene glycol, polyethylene glycol and polypropylene glycol.

25. A topical composition in accordance with claim 24 wherein said nonvolatile solvent component is propylene glycol.

26. A topical composition in accordance with claim 1 wherein the buffer is selected from the group consisting of citrate, phosphate and borate buffer systems and combinations thereof.

27. A topical composition in accordance with claim 26 wherein the buffer is a phosphate-citrate buffer system.

28. A topical composition in accordance with claims 2 and 16 wherein the buffer maintains the pH of the system to be at least 0.5 units above the pKa of the topically active pharmaceutical compound or drug when the topically active pharmaceutical compound or drug is basic.

29. A topical composition in accordance with claims 3 and 16 wherein the buffer maintains the pH of the system to be at least 0.5 units below the pKa of the topically active pharmaceutical compound or drug when the topically active pharmaceutical compound or drug is acidic.

30. A topical composition in accordance with claim 1 further comprising optional ingredients including, without limitation, and in any compatible combination, chelators, antioxidants, preservatives, gelling agents, sunscreens, sunblocks, retinoids, benzofuran derivatives, N-acetyl-L-cysteine and derivatives thereof, skin protectants and vitamins.

31. A topical composition in accordance with claim 1 wherein the composition is in the form of a solution, lotion, gel, cream or ointment.

32. A topical composition comprising:

a) about 0.3% ketoconazole,

b) a buffered solvent system consisting of:

i) about 40% to about 45% by weight ethanol,

ii) about 5% to about 15% by weight propylene glycol,

iii) about 45% to about 50% by weight phosphate-citrate buffer.

33. A topical composition in accordance with claim 32 further comprising EDTA, BHT, methylparaben, propylparaben and hydroxypropylcellulose.

34. A topical composition in accordance with claim 32 wherein the composition is in the form of a solution, lotion, gel, cream or ointment.

35. A method for treating seborrheic dermatitis, psoriasis or a combination thereof comprising topically applying the composition of claim 32 to a region of the skin affected with said skin disorder.

36. A topical composition comprising:

a) a topically active pharmaceutical compound or drug comprising a weak base which is poorly soluble in water; and

b) a buffered solvent system comprising:

i) a volatile solvent component;

ii) a nonvolatile solvent component; and

iii) a buffer component which functions to maintain the pH of the composition at least 0.5 units

above the pKa of the topically active pharmaceutical compound or drug.

37. A topical composition comprising:

a) a topically active pharmaceutical compound or drug comprising a weak acid which is poorly soluble in water; and

b) a buffered solvent system comprising:

i) a volatile solvent component;

ii) a nonvolatile solvent component; and

iii) a buffer component which functions to maintain the pH of the composition at least 0.5 units below the pKa of the topically active pharmaceutical compound or drug.

38. A topical composition comprising:

a) a topically active pharmaceutical compound or drug comprising an azole compound; and

b) a buffered solvent system comprising:

i) a volatile solvent component;

ii) a nonvolatile solvent component; and

iii) a buffer component which functions to maintain the pH of the composition at least 0.5 units above the pKa of the topically active pharmaceutical compound or drug.

39. A topical composition comprising:

a) a topically active pharmaceutical compound or drug comprising a weak acid compound selected from the group of non-steroidal anti-inflammatory drugs and retinoic acid; and

b) a buffered solvent system comprising:

i) a volatile solvent component;

ii) a nonvolatile solvent component; and

iii) a buffer component which functions to maintain the pH of the composition at least 0.5 units below the pKa of the topically active pharmaceutical compound or drug.